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New insights into diagnosis and treatment of peanut food allergy

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1. ABSTRACT

Peanut and/or tree nut allergy is a major health concern affecting over 1% of Americans. Although food allergy in general is the most common cause of anaphylaxis treated in emergency departments, reactions to nuts account for a disproportionate amount of deaths from food allergy. Peanut allergy is a Type I hypersensitivity (IgE mediated) immune response. Eight peanut allergens have been identified that are termed as Ara h 1 through Ara h 8. The diagnosis of peanut allergy can often be made or eliminated with a focused history and specific diagnostic testing. There is no effective method to cure peanut allergy. Therefore, the management of patients with peanut allergy focuses on 1) preventing inadvertent ingestions of peanut, 2) recognizing early signs of allergic reactions, and 3) properly treating peanut-induced symptoms should they occur. Epinephrine is clearly indicated for patients experiencing respiratory, cardiovascular, or neurologic compromise. Because inadvertent ingestion of peanut often leads to life threatening reactions and peanut allergy is often long-lived, many investigators are focusing on decreasing clinical reactivity after peanut allergy is established.

2. INTRODUCTION

An early report of food allergy in 1948 noted adverse reactions to corn, wheat, milk, egg and other frequently ingested foods. (1) It was more than 25 years later when double-blind food challenges identified peanut as an important food allergen in children with severe asthma. (2) In the 1980's a main focus of food allergy research was the use of unbiased food challenges to establish a precise diagnosis of food allergy and describe reproducible food-induced symptoms. It was then that peanut was identified as one of the top three food allergens in US children with atopic dermatitis. (3-6) Today, peanut and/or tree nut allergy is a major health concern affecting over 1% of Americans. (7) Although food allergy in general is the most common cause of anaphylaxis treated in emergency departments, reactions to nuts account for a disproportionate amount of deaths from food allergy. (8-10) Since there is no cure for peanut allergy, therapy focuses on peanut avoidance, early recognition of symptoms due to inadvertent ingestions, and pharmacologic treatment of adverse reactions. This approach can be unsatisfying because it does not modify the immune response to peanut, leaving even the most vigilant patient at risk for life-

threatening reactions from inadvertent ingestions of the food. For this reason, these patients are in critical need of a specific treatment for peanut allergy.

3. EPIDEMIOLOGY

As noted with other atopic diseases in westernized cultures, the prevalence of food allergy appears to be on the rise. In children, peanut *sensitization* tripled and *reported* peanut allergy doubled over only a five year period in both the United States and United Kingdom. (7,11) Studies from Canada and the United Kingdom incorporating diagnostic food challenges currently estimate that the prevalence of peanut allergy in young children may be as high as 1.5%. (11,12) The rise in peanut allergy is not limited to children. Data from a third National Health and Nutritional Examination Survey in the United States (collected from 1988 – 1994) indicate that about 8.6.% of Americans are *sensitized* to peanuts (13). Similarly, national surveys suggest that 1.1.% of Americans or three million people are *allergic* to peanuts, tree nuts, or both (14,15).

Methods of food preparation, increased use of antacids, patterns of peanut consumption in pregnant or lactating mothers and in childhood, as well as exposure to medicinal creams containing peanut oil have all been proposed but not confirmed as factors contributing to the recent rise in peanut allergy. (16-22) Data from the Avon Longitudinal Study of Parents and Children, a geographically defined cohort study of 13,971 preschool children, was used to identify those with a convincing history of peanut allergy and the subgroup who reacted to a double-blind peanut challenge (22). Peanut allergy was independently associated with intake of soy milk or soy formula and with the use of skin preparations containing peanut oil, although these results have yet to be confirmed in other studies. The presence of peanuts in the mother's diet prior to delivery has been suggested to be a risk factor for the development of peanut allergy but this finding also has not been replicated (16). The explanation for the increase in the diagnosis of peanut allergy in the past several years has yet to be explained adequately. Allergic disease in general has been shown to have a genetic predisposition although arguably the development of peanut allergy has not been linked to a specific genetic predisposition (16,23,24).

4. PATHOPHYSIOLOGY

Immune responses to allergenic food proteins develop as a result of complex interactions between the food, a variety of effector cells, and their mediators. The majority of acute allergic reactions to foods are due to the engagement of allergen-specific IgE antibody with its high affinity receptor (FcεRI) that is expressed on mast cells and basophils. The overt signs of food allergy, such as urticaria or angioedema, are often the direct result of peanut protein (not carbohydrate, fat, or oil) cross-linking IgE bound to its effector cell. This antigen-specific interaction stimulates a series of events that results in release of cellular mediators and cytokines including histamine, prostaglandins, leukotrienes, and platelet-activating factor. An unexpected finding was elevated plasma histamine levels in patients with atopic dermatitis and positive food challenges but normal serum tryptase levels in patients with food-induced anaphylaxis. (9,25) Other evidence supporting the central role of basophils, rather than mast cells, in IgE-mediated food allergy is that basophils from patients with food allergy and atopic dermatitis have increased spontaneous release of histamine which declines to control levels after the causal food is restricted from the diet. (26) Additionally, tumor necrosis factor (TNF), interleukin-5, and chemokines produced at the local site result in the activation and recruitment of eosinophils. (27).

The manifestation of allergic reactions to foods not only depends upon a humoral response but is largely dependent upon preceding cellular mechanisms which are just being elucidated. The initial introduction of a food allergen generally occurs at the mucosal surface of the gastrointestinal tract. (18) Food proteins are believed to be taken up by specialized epithelial cells, M cells, transferred to antigen presenting cells such as dendritic cells, and processed into peptide fragments presented on the cell surface in the context of class II Major Histocompatibility Complex (MHC) molecules. (28,29) Peptides then are presented to naive T helper (Th) cells via MHC/T cell receptor interaction resulting in Th cell priming and activation. This event in turn initiates humoral and cellular events associated with, in this particular case, peanut allergy. In individuals at risk for allergic disease, the activation of T helper cells results in secretion of cytokines that stimulate B cells to eventually synthesize IgE antibody specific for peanut in the sensitization phase of the immune response. T helper 2 (Th2) cells cause secretion of various interleukins including interleukin-4, interleukin-5, interleukin-9 and interleukin-13.

Peanut antigen stimulates Th2 cells in peanut allergic donors but Th1 cells in children who have either outgrown their peanut allergy or who are tolerant to peanut, similar to that seen after stimulation with nonallergenic food antigens. (30) This observation that the same food stimulates T helper cells with distinct cellular phenotypes predicted by host factors and clinical reactivity suggests that food tolerance in nonatopic patients or resolution of food allergy in atopic ones is accompanied by the development of a Th1 response (high IFNγ, TNFα, and low IL-4, IL-5, IL-13). The skewed Th2 response observed in atopics may manifest early in life as a result of genetic susceptibility and intrauterine exposures. (31) Regulatory cell populations may also play a role in the development of IgE and cell mediated food allergy by failing to induce or maintain oral tolerance, although the exact mechanism remains largely unknown. (18,32-34).

5. PEANUT ALLERGENS

Foods associated with allergic reactions are generally a main component of one's diet early in life and, therefore, differ according to age and societal eating patterns. For example, sesame seed and bird's nest are eaten frequently in Israel and Singapore, respectively. They

are also common food allergens in those countries but peanut allergy is not as common as in the West. (35;36) The major food allergens are glycoproteins, 10-70 kd in size, that are abundant in the allergenic food. Food allergens are generally water-soluble and resistant to heat, acid, and proteolysis which enables them to sensitize the host in the gastrointestinal tract.

Eight peanut allergens have been identified that are termed as Ara h 1 through Ara h 8 (*Arachis hypogaea*). (37-42) Most of the peanut allergens are members of the seed storage protein families. The two peanut allergens that bind IgE in a majority of patients, Ara h 1 and 2, are part of the vicilin and conglutin family of storage proteins, respectively. Ara h 3 - 7 are minor peanut allergens. Ara h 8 is a member of the pathogenesis-related PR-10 family, primarily involved in pollen-associated food allergy. (42) Identification of individual IgE binding sites or epitopes have research utility in characterizing clinical outcomes, in the development of novel treatments, and in developing transgenic plants producing peanut proteins with reduced IgE-binding capabilities. (43-45)

6. CLINICAL PRESENTATION

Peanut allergy is a Type I hypersensitivity (IgE mediated) immune response. There is a spectrum of clinical symptoms mediated by IgE which mainly involve the skin and gastrointestinal tract: urticaria, angioedema, pruritis, nausea, and vomiting, abdominal pain or cramping, and diarrhea. (3-5,46-48) Respiratory and ocular symptoms of IgE-mediated food allergy often accompany skin and gastrointestinal symptoms but rarely occur in isolation. (3,4,46,47,49) Anaphylaxis is the most severe IgE-mediated response to food. This term implies multi-system organ involvement and varies in severity from mild to fatal. (50,51)

The mean age of diagnosis of peanut allergy in children is approximately 14-18 months. (17,52) Symptoms occur following the first known peanut ingestion in 75% of those children. (52,53).The overwhelming majority of the initial reactions involve the skin, approximately one-half the respiratory tract, and a third the gastrointestinal tract. In one study, two organ systems were affected in 31% of initial reactions, and all three systems in 21% of reactions (53). Fortunately, individuals typically do not have life-ending reactions on the first known ingestion. Individuals who have life-threatening and life-ending reactions usually have asthma and frequently have a history of atopy, including food allergy in childhood, and are typically young adolescents to young adults who unknowingly ate a food to which they were allergic. (9,10,54)

7. DIAGNOSIS

The diagnosis of peanut allergy can often be made or eliminated with a focused history and specific diagnostic testing. The most supportive clinical evidence of peanut allergy includes immediate and reproducible symptoms after ingestion. Most reactions begin within seconds or minutes but may occur up to two hours after eating peanut. If allergy is suspected, peanut is then generally avoided but reproducibility of symptoms may still be assessed if there were previous ingestions or subsequent inadvertent ones. Other factors to consider for the diagnosis of peanut allergy include 1) quantity of peanut required to provoke symptoms, 2) detailed description of symptoms, 3) other foods ingested prior to development of symptoms, and 4) length of time since the last reaction or ingestion of peanut. (49)

Reproducible symptoms suggesting involvement of IgE such as urticaria, repetitive vomiting, or angioedema that occur within two hours of ingestion of peanut support the diagnosis of peanut allergy. In those cases, laboratory techniques that detect peanut-specific IgE are utilized to confirm the diagnosis. They include *in vivo* allergy skin prick tests and *in vitro* assays. Allergy skin testing is easily and safely performed, even in small infants, by applying purified food extract (1:10 or 1:20 w/v) by the prick or puncture technique. (47,55)

Allergy skin prick tests with food extracts are very sensitive but they lack specificity. (56). In patients with atopic dermatitis, the sensitivity of a peanut skin test is 100% but the specificity is only 58%. (5) And the positive predictive value of a peanut skin test is only 44% but the negative predictive value is 100%. (5) In other words, a positive skin test indicates that the patient has been sensitized, but is not definitively allergic, to peanut and a properly placed negative skin test effectively rules out peanut allergy. Because the specificity and positive predictive values are poor, interpretation of allergy skin tests requires clinical correlation to distinguish sensitization from allergy. In this regard, a positive skin test in a patient who eats peanut without adverse symptoms indicates asymptomatic sensitization. On the other hand, with anaphylaxis after ingestion of a single peanut, a positive skin test sufficiently confirms the diagnosis but a negative skin test should stimulate further evaluation.

Food-specific IgE may also be detected by *in vitro* methods including radioallergosorbent tests (RAST) or enzyme-linked immunosorbent assays (ELISA). In general, they are no better able to predict reactions on double blind, placebo controlled food challenges (DBPCFC) than are skin prick tests. (5) A modified in vitro assay, CAP System FEIA (Pharmacia Diagnostics; Uppsala, Sweden) increases the allergen binding capacity of previous techniques and quantitates the results as kilounits of allergen-specific IgE per liter (kUA/L). (56)

This quantitative method is more sensitive than previous qualitative or semi-quantitative ones. More importantly, a diagnostic level has been established for peanut that correlates well with positive outcomes on oral food challenges. (56;57) With a compatible history, a result greater than 14 kU/L (results range from <0.3.5 to >100 kU/L) supports the diagnosis of peanut allergy. As with allergy skin prick tests, negative serum tests for IgE do not always exclude peanut allergy so that a convincing history should not be disregarded.

It is important to note that, although the *likelihood* of clinical reactivity increases with the size of the skin test reaction and level of food-specific IgE, they have no correlation with the severity of the reaction. (56)This point is important for patients and parents to understand so that those with higher peanut-specific IgE levels are not overwhelmed by the fear of anaphylaxis and those with lower levels are not tempted to stray from a strict peanut-elimination diet. Recent studies show that patterns of epitope binding may correlate with the severity of clinical reactions to peanut. (43,44) IgE binding to many epitopes correlated with a history of multisystem reactions to peanut whereas IgE binding to only a few epitopes correlated with reactions limited to the skin. Assays using recombinant allergens may be more sensitive and prove to be useful for diagnosing peanut allergy. (58-60) Skin prick extracts using recombinant peanut allergens are not yet commercially available but are under investigation. The skin prick test size or IgE level to recombinant peanut allergens do not correlate with clinical symptoms but, like patterns of epitope binding, polysensitization to them may predict more severe symptoms. (60) Recent work on component resolved diagnosis suggests that in the future, with the application of understanding the hypersensitivity response to individual allergens such as Ara h 2, we may be able to determine the likelihood of the severity of the disease as well as the long lasting nature for that particular individual. (61)

Results lower than 14 kU/L do not indicate that peanut may be ingested safely. However, subdiagnostic levels combined with a convincing history of immediate IgE-type reactions may support the diagnosis of peanut allergy and justify the need to follow a strict exclusion diet. Those with low or undetectable IgE levels to peanut, especially if they have questionable clinical reactions, should undergo a supervised oral food challenge to determine clinical reactivity. Greater than 50% of patients with a peanut IgE level < 2 kU/L will have a negative peanut challenge. (62,63)

Food challenges are performed by feeding the patient sequential, graded amounts of peanut and carefully observing for adverse effects. The initial serving size is typically less than that required to elicit symptoms (25-500 mg) and doses are increased at intervals longer than that reported between ingestion and onset of symptoms (15-60 minutes). Tolerance of 8-10 grams of peanut flour or two tablespoons of peanut butter provides strong evidence against allergy (one peanut is equivalent to 300 mg of protein). Depending upon the circumstances, oral food challenges may be open, single-blind, or double-blind. (64)

When the patients are carefully selected and the challenge is performed according to standard protocols, oral food challenges are safe procedures. Although positive reactions to oral food challenges are not infrequent, most reactions are not severe and require no treatment or antihistamine only. (49,65) Only 10% of patients failing peanut challenges required epinephrine. (65) The majority of symptoms observed in peanut challenges were cutaneous or gastrointestinal; patients failing peanut challenges were more likely to have oral and upper respiratory symptoms compared to other foods. It is reassuring that patients failing peanut challenges were not more likely to have more severe symptoms than those failing milk, egg, soy or wheat challenges.

8. TREATMENT

There is no effective method to cure peanut allergy. Therefore, the management of children with peanut allergy focuses on 1) preventing inadvertent ingestions of peanut, 2) recognizing early signs of allergic reactions, and 3) properly treating peanut-induced symptoms should they occur.

Compliance with a food elimination diet is time-consuming, inconvenient, and requires a great deal of education and commitment on the part of the patient and all caregivers. Parents and caregivers must scrutinize all food labels for the presence of peanut. Although peanut is often an obvious component of processed foods, it can also be found in unexpected items such as gravy or salsa that are thickened with such a small amount of peanut butter that it is not detected by taste or smell. Most patients with peanut allergies will avoid the ingestion of peanut oil, although highly processed oils do not contain peanut protein and can be safely consumed by such patients. (66) Cold pressed or extracted peanut oils do contain peanut protein and could possibly induce an allergic reaction.

Children with peanut allergy are faced with many social restrictions due to the potentially life-threatening nature of their disease. The quality of life for these children is significantly impaired, even compared to children with other chronic diseases including diabetes (67). For example, they should consider avoiding high risk places where contamination with peanut is likely, including bakeries and ice cream parlors, as well the ingestion of unlabeled desserts and candies. It is important to give patients and families a written plan with the specifics of their management both for acute and chronic treatment (68). Educational materials are available through many organizations such as the Anaphylaxis Campaign (website: www.anaphylaxis.org.uk/) and the Food Allergy & Anaphylaxis Network (website: www.foodallergy.org). These organizations and their web sites are invaluable resources for patients, families and medical personnel. Registered dieticians can often provide additional educational assistance on an ongoing basis. Additionally it is also important to consider having the patient wear a bracelet or necklace noting their allergy.

Even the most vigilant patients accidentally ingest a food to which they are sensitive. (69) These inadvertent exposures will result in an allergic reaction in the average patient every three to five years, with a new study showing an annual incident rate of 14% (54,70) These accidents occur most frequently away from the home such as in daycare, school, or restaurants where a person unfamiliar with food allergy may be responsible for determining the safety of the food. (9,10) Cross-contamination of food may also lead to inadvertent

ingestion of restricted foods. The food may be contaminated during the manufacture process if the same equipment used to process foods with and without a food allergen is not cleaned adequately between batches. Other settings where cross-contamination is likely to occur include bulk food bins, salad bars, or during the preparation of different foods with shared cooking utensils.

Fortunately, there is little risk from topical or inhaled environmental exposures to food allergens; generally, one must ingest peanut to have a systemic, life-threatening allergic reaction. (71,72) After applying peanut butter to the skin of peanut-allergic patients, there were no systemic reactions and one third of subjects had localized erythema or itching only. No patients had reactions to inhaled challenges with peanut butter. The risk of unanticipated exposures due to peanut allergen in the environment also appears to be low because it is removed from hands and surfaces with standard cleaning procedures. Furthermore, airborne levels were not detected around subjects who ate peanut butter and peanuts, even after shelling them. The real risk of inhaling peanut protein in airplanes with recirculated air is difficult to determine and underscores the importance of always being prepared to treat reactions (73).

Incorrect or ambiguous food labels may result in accidental ingestion of the offending allergen. The United States Food and Drug Administration requires food manufacturers to declare all functional ingredients on food labels. The Food Allergen Labeling and Consumer Protection Act (FALCPA) requires food manufacturers to explicitly state the presence of the eight major food allergens: milk, egg, wheat, soybean, peanut, tree nuts, fish and shellfish. Under this legislation, the language must be understandable to the average consumer and colorings, flavorings, or any other additives will not be exempt.

Some food manufacturers also use advisory labels such as “may contain peanut”, “manufactured on shared equipment with peanut”, or “manufactured in the same facility with peanuts” in order to warn consumers of the potential risk of peanut exposure. Practitioners often appropriately advise peanut allergic patients to avoid these products but the increase in foods with this vague warning has led patients to be complacent about excessive dietary restrictions, especially in those who previously tolerated the food in question. Although the majority of foods with these labels were actually free of peanut, the <10% containing clinically significant levels of peanut protein pose a threat to peanut allergic patients who ignore advisory labels. (74)

Because inadvertent food ingestions can not always be avoided, patients and their caregivers must be equipped to manage acute food-induced reactions. Individualized treatment plans should be prepared in advance and medications readily available. Epinephrine (0.01 mg/kg aqueous epinephrine 1:1000, maximum dose 0.3-0.5 ml) is the drug of choice for the treatment of food-induced anaphylaxis. (51) Delayed administration of this medication correlates with poor outcomes. (9,10,75) Prompt elevations in plasma epinephrine levels are desirable and achieved more readily after intramuscular injection compared to the subcutaneous route. (76,77)

The EpiPen™ (Dey; Napa, CA) contains a fixed dose of epinephrine in a self-injectable device allowing for rapid, intramuscular administration of the medication. Use of an auto-injector is preferable to withdrawing a designated dose of the medication from an ampule prior to injection because the latter method leads to imprecise dosing and delayed administration. (78) The EpiPen Jr™, containing 0.15mg epinephrine, is prescribed for children 15-30 kg while the EpiPen™, containing 0.3mg epinephrine, is prescribed for children >30 kg. Another device, Twinject™ (Verus Pharmaceuticals, Inc.; San Diego, CA), is also available for self-administration of epinephrine. It contains one of the same two fixed doses as the EpiPen™ but has the option to administer a second dose of epinephrine from the same device. The first dose is administered with an auto-injector, the second is injected manually with a pre-filled injector.

Epinephrine is clearly indicated for patients experiencing respiratory, cardiovascular, or neurologic compromise but more specific guidelines for its use have not been established. (51) The importance of gastrointestinal symptoms is particularly controversial because they may signify a more serious reaction or quickly resolve without any medical intervention. (50) In uncerta*in situ*ations the decision to treat with epinephrine not only depends upon the symptoms that the patient is acutely experiencing but also upon factors known to correlate with outcomes of food-induced anaphylaxis. A history of a previous life-threatening reaction, allergy to peanut, concomitant diagnosis of asthma, or a reaction occurring outside of the home all correlate with poor outcomes; patients with these risk factors should be treated aggressively. These factors may also be considered when determining which of the two fixed doses of epinephrine to prescribe for children. (51,79) Children between 20 and 30 kg with risk factors for severe food-induced anaphylaxis may be prescribed 0.3 mg which will provide more epinephrine than the recommended 0.01 mg/kg rather than a subtherapeutic dose. (51) The importance of asthma as a risk for fatal food-induced anaphylaxis is particularly important and not limited to those with poorly controlled respiratory symptoms.

9. FUTURE DIRECTIONS

Because inadvertent ingestion of peanut often lead to life threatening reactions and peanut allergy is often long-lived, many investigators are focusing on decreasing clinical reactivity after peanut allergy is established. A Phase I trial with humanized, monoclonal anti-IgE antibody (TNX-901) proved beneficial for some patients with peanut allergy by increasing the threshold dose of peanut required to elicit symptoms but it remains under investigation for the treatment of peanut allergy. (80) Subcutaneous immunotherapy demonstrated efficacy in some patients with peanut allergy but significant adverse reaction rates made it unsuitable for clinical use. (81,82) Therefore, immunotherapy utilizing alternative routes of allergen

administration with a more favorable risk benefit ratio is desirable.

Immunotherapy by the sublingual route (SLIT) was successful in adults with hazelnut allergy and has prompted studies of its use in peanut allergic patients. (83,84). Although the mainstay of therapy for peanut allergy is avoidance of the allergen, some investigators believe that routine ingestion of increasingly larger amounts of peanut may actually induce tolerance. This method of treatment, oral immunotherapy (OIT), has shown promise for egg allergy. (85) Similar studies of OIT for peanut allergy, which differs significantly from egg allergy in that it is not usually outgrown, are now being conducted (86-88). The potential of anaphylaxis during OIT is significant, so this therapy should not be attempted as yet. These studies hold promise for the possibility of at least hyposensitization (raising the threshold of the amount of peanut that it would take to cause a life-threatening allergic reaction) or desensitization (preventing an allergic reaction while peanut was routinely ingested). Whether these types of treatments are likely to cause clinical tolerance to develop and persist after active treatment is discontinued remains to be seen. It is extremely likely that in the next five years there will be some type of specific immunotherapy available for peanut allergic individuals.

The main risk of immunotherapy, regardless of the route of administration, is anaphylaxis to the administration of whole allergens. Novel immunotherapeutic strategies aim to reduce this risk while still altering the immune system's response to the specific allergen. An example is the use of overlapping T-cell peptides for cat allergy. These short peptides do not bind IgE and, instead, inhibit allergic reactions to the whole cat allergen. (89,90). An increase in IL-10 production suggests a role for T regulatory cells in tolerance induction using T-cell peptides. The use of engineered peanut allergens in studies has similar utility to the short peptides in that the mutated peanut allergens (recombinant Ara h 1, 2 and 3) bind less peanut-specific IgE but retain the critical T-cell epitopes needed for effective immunotherapy (91-94). Another method of immunotherapy that is well tolerated and may produce greater clinical benefit beyond the period of active therapy utilizes heat-killed Listeria or E. coli (HKL, HKE) as an adjuvant for the peanut protein or modified peanut allergen. Immunotherapy with HKL or HKE and peanut allergen in dogs and mice rapidly induced the innate immune system via toll-like receptors and simultaneously modified adaptive immunity with a decline in peanut-specific IgE production. (94,95) Clinical correlates in the animals included reduced skin test reactivity to peanut and mild or no symptoms after oral food challenges.

Cytokine-modulated immunotherapy, immunostimulatory sequence-conjugated protein-modulated immunotherapy, and plasmid DNA immunotherapy also attempt to curb the Th2-type response and induce tolerance by increased Th1 and T regulatory cytokine production responses to peanut allergen. (96-98) Other studies have shown the possibility of utilizing similar or cross-reacting proteins in soybeans for immunotherapy in peanut allergic mice. (99)

10. NATURAL HISTORY

Historically, allergy to peanut is not thought to be outgrown but the natural history of peanut allergy in young patients is still evolving. (100,101) It is now apparent that about 20% of children with peanut allergy may eventually develop tolerance. (63,102;103) The current approach to children with newly-diagnosed peanut allergy is to measure peanut-specific IgE levels annually and to perform an oral food challenge in patients 4 years of age or older if the peanut-specific IgE level decreases to < 2 kU_A/L. IgE levels < 2 kU_A/L are associated with a 50% rate of negative challenges. (62) Children who outgrow their sensitivity to peanut are then advised to consume peanut routinely and have epinephrine available until peanut has been tolerated for one year because up to 8% may develop a recurrence of their allergy. (104-106) Children > 5 years of age whose peanut-specific IgE level remains > 15 kU_A/L or who fail an oral challenge at a lower level are less likely to develop tolerance.

Favorable, but not conclusive, factors for outgrowing peanut allergy include the absence of atopic dermatitis or other food allergies, mild peanut-induced symptoms limited to the skin, and a small initial skin prick response (< 6 mm) or low (<10 kU_A/L) peanut-specific IgE level. In the future, patterns of epitope binding may be able to distinguish patients who are not likely to outgrow their allergy to peanut. (43)

An interesting and poorly understand observation of peanut allergic patients is their high likelihood of developing allergy to tree nuts (up to 50%), which are not botanically related, but not to other legumes (5%). (107) Due to the high rate of co-allergy and the risk of contamination with peanut protein, patients with peanut allergy are often counseled to also avoid eating tree nuts. Although allergy skin prick tests and food-specific IgE levels may indicate sensitization to different foods in the same botanical family (peanut and soybean), patients rarely have positive food challenges to related foods. (3,4,108) Therefore, they do not require strict avoidance of other legumes (green beans, green pea, lentils, etc) unless there is clinical evidence of allergy. Furthermore, screening for allergy to other legumes in the absence of clinical symptoms may not be particularly useful for peanut allergic patients because of the high rate of false positives due to allergen cross-reactivity. Clinical studies did not include large batteries of legumes, and it may be that particular types are more allergenic or cross-reactive. In more recent studies from Europe there appears a larger number of children with peanut allergy who also have clinical allergy to lupine. (109)

Given the rising prevalence of food allergy, interest in preventing its onset is increasing among parents and practitioners. Based on interpretations of existing studies for the primary prevention of food allergy in high-risk infants, the American Academy of Pediatrics (AAP)

has encouraged exclusive breastfeeding for 4 to 6 months and supplementing with or weaning to an extensively hydrolyzed casein formula.

The most consistent benefit from prolonged breastfeeding and hypoallergenic diets in infancy is a decrease in infantile atopic dermatitis and cow's milk allergy. (110,111) Maternal dietary interventions during the third trimester and lactation have not convincingly shown decreased cow's milk allergy in infancy or decreased food allergy, atopic dermatitis, or asthma at older ages. (110,112) Furthermore, dietary manipulations after 4-6 months of age such as delaying introduction of egg, cow's milk, peanut, and/or fish, are not likely to prevent or delay the development of atopy. However, the American Academy of Pediatrics currently advises high risk patients to delay introduction of peanuts beyond the third year of life. (48) It is likely these guidelines will be changed because of the lack of evidence in human studies that these recommendations are beneficial. In fact, others postulate that the lack of ingestion early in life may actually increase the possibility of becoming sensitized to peanuts. (22,113)There is the possibility that in children the introduction of small amounts of peanuts early in life may prevent sensitization, such that ingestion of Bamba (a peanut containing snack) may produce allergic tolerance to peanut proteins. (114) There are other observations suggesting that the prevalence of peanut allergy in infancy is low in populations that consume peanut containing snacks during the first year of life. (35,115) Further work is needed to define what role, if any, early peanut exposure plays in the development of allergy.

11. SUMMARY

The public's awareness of peanut allergy has increased significantly over recent years. Children are experiencing allergic reactions to peanut at an earlier age. (17) These two observations seem difficult to reconcile because the obvious response to knowing about the high frequency of adverse reactions to a food would be to avoid it, especially in young children or those with a family history of allergy. Therefore, the earlier age of diagnosis may merely reflect recognition of adverse symptoms on the first ingestion rather than on subsequent ones. It is also possible that peanut protein has become more of a staple in our diets or is present in more processed foods, both of which would make it difficult to avoid. Even those with known allergy to foods have frequent accidental ingestions that may lead to life-threatening or fatal reactions. (9, 69,70) Regardless, avoidance of allergenic foods does not effectively prevent food allergy. Therefore, if food allergy can not be prevented, and subsequent food-induced reactions are likely, efficacious, safe methods to modulate established immune responses to peanut are desirable.

12. REFERENCES

1. Randolph TG. Food allergy. *M Clin North America* 245 (1948)

2. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J Allergy Clin Immunol* 58, 500-515 (1976)

3. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 107, 669-675 (1985)

4.Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 113, 447-451 (1988)

5. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 74, 26-33 (1984)

6. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 71, 473-480 (1983)

7. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 112, 1203-1207 (2003)

8. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: A population-based study. *J Allergy Clin Immunol* 104, 452-456 (1999)

9. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 327, 380-384 (1992)

10. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 107,191-193 (2001)

11. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. *J Allergy Clin Immunol* 110,784-789 (2002)

12. Kagan RS, Joseph L, Dufresne C, Gray-Donald K, Turnbull E, Pierre YS, Clarke AE. Prevalence of peanut allergy in primary-school children in Montreal, Canada. *J Allergy Clin Immunol* 112, 1223-1228 (2003)

13. Arbes SJ, Jr., Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 116, 377-383 (2005).

14. Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 103, 559-562 (1999)

15. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 112,1203-1207 (2003)

16. Frank L, Marian A, Visser M, Weinberg E, Potter PC. Exposure to peanuts *in utero* and in infancy and the development of sensitization to peanut allergens in young children. *Pediatr Allergy Immunol* 10, 27-32 (1999)

17. Green TD, LaBelle VS, Steele PH, Kim EH, Lee LA, Mankad VS, Williams LW, Anstrom KJ, Burks AW. Clinical characteristics of Peanut-Allergic Children: Recent Changes. *Pediatrics* 120, 1304-1310 (2007)

18. Chehade M, Mayer L. Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol* 115, 3-12 (2005)

19. Maleki SJ, Viquez O, Jacks T, Dodo H, Champagne ET, Chung SY, Landry SJ. The major peanut allergen, Ara h 2, functions as a trypsin inhibitor, and roasting enhances this function. *J Allergy Clin Immunol* 112, 190-195 (2003)

20. Untersmayr E, Scholl I, Swoboda I, Beil WJ, Förster-Waldl E, Walter F, Riemer A, Kraml G, Kinaciyan T, Spitzauer S, Boltz-Nitulescu G, Scheiner O, Jensen-Jarolim E. Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy model in BALB/c mice. *J Allergy Clin Immunol* 112, 616-623 (2003)

21. Untersmayr E, Bakos N, Scholl I, Kundi M, Roth-Walter F, Szalai K, Riemer AB, Ankersmit HJ, Scheiner O, Boltz-Nitulescu G, Jensen-Jarolim E. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J* 19, 656-658 (2005)

22. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 348, 977-985 (2003)

23. Sicherer SH, Furlong TJ, Maes HH, Desnick RJ, Sampson HA, Gelb BD. Genetics of peanut allergy: a twin study. *J Allergy Clin Immunol* 106, 53-56 (2000)

24. Shreffler WG, Charlop-Powers Z, Sicherer SH. Lack of association of HLA class II alleles with peanut allergy. *Ann Allergy Asthma Immunol* 96, 865-869 (2006)

25. Sampson HA, Jolie PL. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 311, 372-376 (1984)

26.Sampson HA, Broadbent KR, Bernhisel-Broadbent J. Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. *N Engl J Med* 321, 228-232 (1989)

27. Gleich GJ. Mechanisms of eosinophil-associated inflammation. *J Allergy Clin Immunol* 105, 651-663 (2000)

28. Prioult G, Nagler-Anderson C. Mucosal immunity and allergic responses: lack of regulation and/or lack of microbial stimulation? *Immunol Rev* 206, 204-218 (2005)

29. Strobel S, Mowat AM. Oral tolerance and allergic responses to food proteins. *Curr Opin Allergy Clin Immunol* 6, 207-213 (2006)

30.Turcanu V, Maleki SJ, Lack G. Characterization of lymphocyte responses to peanuts in normal children, peanut-allergic children, and allergic children who acquired tolerance to peanuts. *J Clin Invest* 111, 1065-1072 (2003)

31. Warner JA, Warner JO. Early life events in allergic sensitisation. *Br Med Bull* 56, 883-893 (2000)

32. Beyer K, Castro R, Birnbaum A, Benkov K, Pittman N, Sampson HA. Human milk-specific mucosal lymphocytes of the gastrointestinal tract display a TH2 cytokine profile. *J Allergy Clin Immunol* 109, 707-713 (2002)

33. Perez-Machado MA, Ashwood P, Thomson MA, Latcham F, Sim R, Walker-Smith JA, Murch SH. Reduced transforming growth factor-beta1-producing T cells in the duodenal mucosa of children with food allergy. *Eur J Immunol* 33, 2307-2315 (2003)

34. Karlsson MR, Rugtveit J, Brandtzaeg P. Allergen-responsive CD4+CD25+ regulatory T cells in children who have outgrown cow's milk allergy. *J Exp Med* 199, 1679-1688 (2004)

35. Dalal I, Binson I, Reifen R, Amitai Z, Shohat T, Rahmani S, Levine A, Ballin A. Food allergy is a matter of geography after all: sesame as a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel. *Allergy* 57, 362-365 (2002)

36. Goh DL, Lau YN, Chew FT, Shek LP, Lee BW. Pattern of food-induced anaphylaxis in children of an Asian community. *Allergy* 54, 84-86 (1999)

37. Burks AW, Williams LW, Helm RM, Connaughton C, Cockrell G, O'Brien T. Identification of a major peanut allergen, Ara h I, in patients with atopic dermatitis and positive peanut challenges. *J Allergy Clin Immunol* 88, 172-179 (1991)

38. Burks AW, Williams LW, Connaughton C, Cockrell G, O'Brien TJ, Helm RM. Identification and characterization of a second major peanut allergen, Ara h II, with use of the sera of patients with atopic dermatitis and positive peanut challenge. *J Allergy Clin Immunol* 90, 962-969 (1992)

39. Burks AW, Cockrell G, Connaughton C, Karpas A, Helm RM. Epitope specificity of the major peanut allergen, Ara h II. *J Allergy Clin Immunol* 95, 607-611 (1995)

40. Burks AW, Cockrell G, Stanley JS, Helm RM, Bannon GA. Recombinant peanut allergen Ara h I expression and IgE binding in patients with peanut hypersensitivity. *J Clin Invest* 96, 1715-1721 (1995)

41. Koppelman SJ, Knol EF, Vlooswijk RA, Wensing M, Knulst AC, Hefle SL, Gruppen H, Piersma S. Peanut allergen Ara h 3: isolation from peanuts and biochemical characterization. *Allergy* 58, 1144-1151 (2003)

42. Mittag D, Akkerdaas J, Ballmer-Weber BK, Vogel L, Wensing M, Becker WM, Koppelman SJ, Knulst AC, Helbling A, Hefle SL, Van Ree R, Vieths. Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. *J Allergy Clin Immunol* 114, 1410-1417 (2004)

43. Beyer K, Ellman-Grunther L, Jarvinen KM, Wood RA, Hourihane J, Sampson HA. Measurement of peptide-specific IgE as an additional tool in identifying patients with clinical reactivity to peanuts. *J Allergy Clin Immunol* 112, 202-207 (2003)

44. Shreffler WG, Beyer K, Chu TH, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, *in vitro* IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 113, 776-782 (2004)

45. Moseley BE. How to make foods safer--genetically modified foods. *Allergy* 56, 61-63 (2001)

46. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 117, 561-567 (1990)

47. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. *J Allergy Clin Immunol* 62, 327-334 (1978)

48. Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 113, 805-819 (2004)

49. Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, Bush RK, Metcalfe DD. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 82, 986-997 (1988)

50. Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 114, 371-376 (2004)

51. Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 111, 1601-1608 (2003)

52. Sicherer SH, Furlong TJ, Munoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol* 108, 128-132 (2001)

53. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 102, e6 (1998)

54. Burks W. Food allergens. *Clin Allergy Immunol* 18, 319-337 (2004)

55. Myers LA. Skin tests, *In vitro* tests. In: Allergy in Primary Care. Eds: Altman LC, Becker JW, Williams PV. *W.B. Saunders Company*, Philadelphia (2000)

56. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 100, 444-451 (1997)

57. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 107, 891-896 (2001)

58. Mari A, Ballmer-Weber BK, Vieths S. The oral allergy syndrome: improved diagnostic and treatment methods. *Curr Opin Allergy Clin Immunol* 5, 267-273 (2005)

59. Pastorello EA, Robino AM. Clinical role of lipid transfer proteins in food allergy. *Mol Nutr Food Res* 48, 356-362 (2004)

60. Astier C, Morisset M, Roitel O, Codreanu F, Jacquenet S, Franck P, Ogier V, Petit N, Proust B, Moneret-Vautrin DA, Burks AW, Bihain B, Sampson HA, Kanny G . Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J Allergy Clin Immunol* 118, 250-256 (2006)

61. Bublin M, Lauer I, Oberhuber C, Alessandri S, Briza P, Radauer C, Himly M, Breiteneder H, Vieths S, Hoffmann-Sommergruber K.Production and characterization of an allergen panel for component-resolved diagnosis of celery allergy.*Mol Nutr Food Res*. 2 (2008)

62. Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 114, 144-149 (2004)

63. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: Resolution and the possibility of recurrence. *J Allergy Clin Immunol* 112, 183-189 (2003)

64. Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol* 10, 226-234 (1999)

65. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. *J Allergy Clin Immunol* 114, 1164-1168 (2004)

66. Hourihane JO, Bedwani SJ, Dean TP, Warner JO. Randomised, double blind, crossover challenge study of allergenicity of peanut oils in subjects allergic to peanuts. *BMJ* 314, 1084-1088 (1997)

67. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol* 14, 378-382 (2003)

68. Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. *Lancet* 357, 111-115 (2001)

69. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 83, 900-904 (1989)

70. Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y, Clarke A. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol* 118, 466-472 (2006)

71. Perry TT, Conover-Walker MK, Pomes A, Chapman MD, Wood RA. Distribution of peanut allergen in the environment. *J Allergy Clin Immunol* 113, 973-976 (2004)

72. Simonte SJ, Ma S, Mofidi S, Sicherer SH. Relevance of casual contact with peanut butter in children with peanut allergy. *J Allergy Clin Immunol* 112, 180-182 (2003)

73. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. Self-reported allergic reactions to peanut on commercial airliners. *J Allergy Clin Immunol* 104, 186-189 (1999)

74. Hefle SL, Furlong TJ, Niemann L, Lemon-Mule H, Sicherer S, Taylor SL.Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *J Allergy Clin Immunol* 120, 171-6 (2007)

75. Yunginger JW, Sweeney KG, Sturner WQ, Giannandrea LA, Teigland JD, Bray M, Benson PA, York JA, Biedrzycki L, Squillace DL. Fatal food-induced anaphylaxis. *JAMA* 260, 1450-1452 (1988)

76. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 101, 33-37 (1998)

77. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 108, 871-873 (2001)

78. Simons FE, Chan ES, Gu X, Simons KJ. Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical?. *J Allergy Clin Immunol* 108, 1040-1044 (2001)

79. Simons FE. First-aid treatment of anaphylaxis to food: focus on epinephrine. *J Allergy Clin Immunol* 113, 837-844 (2004)

80. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR Jr; Avon Longitudinal Study of Parents and Children Study Team. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 348, 986-993 (2003)

81. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 90, 256-262 (1992)

82. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 99, 744-751 (1997)

83. Enrique E, Pineda F, Malek T, Bartra J, Basagaña M, Tella R, Castelló JV, Alonso R, de Mateo JA, Cerdá-Trias T, San Miguel-Moncín Mdel M, Monzón S, García M, Palacios R, Cisteró-Bahíma A. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 116, 1073-1079 (2005)

84. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 60, 4-12 (2005)

85. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, Steele PH, Pons L, Helm RM, Lee LA, Burks AW. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 119, 199-205 (2007)

86. Buchanan A, Scurlock AM, Jones SM, Christie L, Althage KM, Pons L, Steele PH, Burks W. Oral des ensitization and induction of tolerance in peanut-allergic children. *J Allergy Clin.Immunol* 117, S327 (2006)

87. Mansfield L. Successful oral desensitization for systemic peanut allergy. *Ann Allergy Asthma Immunol* 97, 266-267 (2006)

88. Patriarca G, Nucera E, Pollastrini E, Roncallo C, De Pasquale T, Lombardo C, Pedone C, Gasbarrini G, Buonomo A, Schiavino D. Oral rush desensitization in peanut allergy: a case report. *Dig Dis Sci* 51, 471-473 (2006)

89. Oldfield WL, Larche M, Kay AB. Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: a randomised controlled trial. *Lancet* 360, 47-53 (2002)

90. Verhoef A, Alexander C, Kay AB, Larche M. T cell epitope immunotherapy induces a CD4+ T cell population with regulatory activity. *PLoS Med* 2, e78 (2005)

91. King N, Helm R, Stanley JS, Vieths S, Lüttkopf D, Hatahet L, Sampson H, Pons L, Burks W, Bannon GA. Allergenic characteristics of a modified peanut allergen. *Mol Nutr Food Res* 49, 963-971 (2005)

92. Burks AW, King N, Bannon GA. Modification of a major peanut allergen leads to loss of IgE binding. *Int Arch Allergy Immunol* 118, 313-314 (1999)

93. Rabjohn P, Helm EM, Stanley JS, West CM, Sampson HA, Burks AW, Bannon GA. Molecular cloning and

epitope analysis of the peanut allergen Ara h 3. *J Clin Invest* 103, 535-542 (1999)

94. Li XM, Srivastava K, Grishin A, Huang CK, Schofield B, Burks W, Sampson HA. Persistent protective effect of heat-killed Escherichia coli producing "engineered," recombinant peanut proteins in a murine model of peanut allergy. *J Allergy Clin Immunol* 112, 159-167 (2003)

95. Frick OL, Teuber SS, Buchanan BB, Morigasaki S, Umetsu DT. Allergen immunotherapy with heat-killed Listeria monocytogenes alleviates peanut and food-induced anaphylaxis in dogs. *Allergy* 60, 243-250 (2005)

96. Li XM, Sampson HA. Novel approaches to immunotherapy for food allergy. *Clin Allergy Immunol* 18, 663-679 (2004)

97. Burks W, Lehrer SB, Bannon GA. New approaches for treatment of peanut allergy: chances for a cure. *Clin Rev Allergy Immunol* 27, 191-196 (2004)

98. Palmer K, Burks W. Current developments in peanut allergy. *Curr Opin Allergy Clin Immunol* 6, 202-206 (2006)

99. Pons L, Ponnappan U, Hall RA, Simpson P, Cockrell G, West CM, Sampson HA, Helm RM, Burks AW. Soy immunotherapy for peanut-allergic mice: modulation of the peanut-allergic response. *J Allergy Clin Immunol* 114, 915-921 (2004)

100. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 115, 23-27 (1989)

101. Wood RA. The natural history of food allergy. *Pediatrics* 111, 1631-1637 (2003)

102. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol* 107, 367-374 (2001)

103. Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *BMJ* 316, 1271-1275 (1998)

104. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. Peanut allergy: recurrence and its management. *J Allergy Clin Immunol* 114, 1195-1201 (2004)

105. Busse PJ, Nowak-Wegrzyn AH, Noone SA, Sampson HA, Sicherer SH. Recurrent peanut allergy. *N Engl J Med* 347, 1535-1536 (2002)

106. Eigenmann PA, Caubet JC, Zamora SA. Continuing food-avoidance diets after negative food challenges. *Pediatr Allergy Immunol* 17, 601-605 (2006)

107. Sicherer SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 108, 881-890 (2001)

108. Burks AW, James JM, Hiegel A, Wilson G, Wheeler JG, Jones SM, Zuerlein N. Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 132, 132-136 (1998)

109. Moneret-Vautrin DA, Guerin L, Kanny G, Flabbee J, Fremont S, Morisset M. Cross-allergenicity of peanut and lupine: the risk of lupine allergy in patients allergic to peanuts. *J Allergy Clin Immunol* 104, 883-888 (1999)

110. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 95, 1179-1190 (1995)

111. Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomised prospective study. *BMJ* 300, 837-840 (1990)

112. Hattevig G, Sigurs N, Kjellman B. Effects of maternal dietary avoidance during lactation on allergy in children at 10 years of age. *Acta Paediatr* 88, 7-12 (1999)

113. Lack G, Golding J. Peanut and nut allergy. Reduced exposure might increase allergic sensitisation. *BMJ* 313, 300 (1996)

114. Khakoo A, Lack G. Preventing food allergy. *Curr Allergy Asthma Rep* 4, 36-42 (2004)

115. Levy Y, Broides A, Segal N, Danon YL. Peanut and tree nut allergy in children: role of peanut snacks in Israel? *Allergy* 58, 1206-1207 (2003)

Abbreviations: Ara h :Arachis hypogaea, DBPCFC : placebo controlled food challenges, ELISA: enzyme-linked immunosorbent assays, FcεRI: high-affinity receptor for immunoglobulin E, HKE: heat-killed E. Coli, HKL: heat-killed Listeria, IFNγ: Interferon gamma, IL: Interleukin, MHC :Major Histocompatibility Complex , OIT: oral immunotherapy, RAST: radioallergosorbent tests, SLIT: Immunotherapy by the sublingual route, Th :T helper , TNF: tumor necrosis factor

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